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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/202,047	12/07/98	ITOH	K 20-4491P

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EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 02/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/202,047	Applicant(s) Itoh et al
	Examiner Larry R. Helms Ph.D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *20 Oct 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-15* is/are pending in the applicat

Of the above, claim(s) *1-5, 10, 11, 14, and 15* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *6-9, 12, and 13* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2 and 5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 6-9 and 12-13, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the special technical feature linking the claims under PCT Rule 13.1 is not destroyed by the Boon et al reference because "Boon et al fails to disclose a protein, that through intracellular degradation, results in peptide fragments that bind to MHC claim I antigens, as well as be recognized by T cells in the binding state." (See page 2 of response) This is not persuasive. As stated in the restriction requirement "Claim 1 is broadly interpreted to mean any protein (SEQ ID NO:2 with more than one substitution, deletion or added residues) that binds MHC class I antigen and which can be recognized by T cells." In addition, claim 1 recites "capable of yielding, through its intracellular decomposition, peptide fragment(s)", which due to the indefinite nature of this phrase the peptide of Boon et al reads on the claim. The polypeptide of Boon et al, which applicants admit is recognized by T cells and can bind to MHC class I antigens (see page 2 of response), would also inherently be capable of producing fragments of the polypeptide which would also bind to MHC class antigens and which would be recognized by T cells. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. In addition, clearly different searches and issues are involved in the examination of each group. The examination of the DNA would be in class 536, subclass

23.1, the polypeptide in class 530, subclass 300, and the antibody in class 530, subclass 387.1. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 1-5, 10, 11, and 14-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

3. Claims 6-9 and 12-13 are under examination.

Claim Objections

4. Claims 6-9 and 12-13 are objected to because of the following informalities: claim 6 is dependent on non-elected claims 1 or 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 6-9 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 6-9 and 12-13 are indefinite for reciting "capable of yielding" in claim 1 or 2 because the exact meaning of the phrase is not clear. Does the phase mean that peptide fragments are produced or not?

b. Claims 6-9 and 12-13 are indefinite for reciting in claims 1 and 2 "through intracellular decomposition" because the exact phrase is not clear. Does the phrase mean the polypeptide is degraded, proteolyzed, processed, etc?

c. Claims 7, 8, 12, and 13 are indefinite for reciting 'functionally equivalent properties" in claims 7 and 8 because the exact meaning of the phrase is not clear. What are the properties that are "functionally equivalent" are they binding, same number of amino acids, etc?

d. Claims 7-8 and 12-13 are indefinite for reciting "derivative" in claims 7 and 8 and "derivate" in claims 12 and 13. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the peptides are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the peptide is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, fragments, chemically

derivatized molecules, or even mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

e. Claims 6-9 and 12-13 are indefinite for reciting "a tumor antigen produced by the expression" in claim 6 because the phase is not clear. The claim is indefinite for not putting forth process steps producing the protein.

f. Claims 6-9 and 12-13 are indefinite for reciting in claim 2 the phrase "under stringent conditions" for it is not known what complete set of conditions are encompassed by the phrase. It is not clear which of the "stringent conditions" described on page 11 of the specification are encompassed by the claims and whether the claims read upon "low" and "high" stringency limitations. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

g. Claims 12-13 are indefinite for reciting "medicine" because the exact meaning of the term is not clear. Does the term mean a "composition" or a "compound"?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6-9 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a tumor antigen protein of SEQ ID NO:2 and peptides

consisting of amino acid residues 749-757, 136-744, 785-793, or 690-698 of SEQ ID NO:2 and compositions comprising such, does not reasonably provide enablement for a tumor antigen protein which is any variant protein of SEQ ID NO:2 which contains any unspecified number of substitutions, deletions, additions, or derivatives or a variant DNA which hybridizes to the DNA of SEQ ID NO:1 under any stringent conditions to produce a protein which would through its intracellular decomposition would be capable of yielding peptides which would bind to MHC class I antigen and which can be recognized by T cells in such binding site and medicines comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any tumor antigen protein or derivatives capable of yielding through intracellular decomposition peptide fragments which can bind to MHC class I antigen and which can be recognized by T cells in such binding site and compositions comprising such. The specification teaches a tumor antigen protein of SEQ ID NO:2 and peptide fragments

having the amino acid sequence of "736-745", "748-757", and "784-793" (see page 36) and "690-698" (see page 37) of SEQ ID NO:2 which when added to KE-4CTL cells produce INF-gamma (see Table 3 and 4). The specification fails to enable any peptides that are produced through "intracellular decomposition" which bind MHC class I antigen and can be recognized by T cells. The specification does not enable any variants of SEQ ID NO:2 or variants of peptides of amino acid residues "736-745", "748-757", "784-793" and "690-698" of SEQ ID NO:2 with the claimed properties.

The claims are not commensurate in scope with the enablement provided in the specification. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino

terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation of the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, and Lin et al conclusively demonstrate.

Moreover, the specification fails to recite under what hybridizing conditions the DNA would anneal to the nucleic acid molecule. Under low stringency conditions, it would be expected that a wide variety of unrelated DNA molecules would be able to anneal to the complementary nucleic acid sequence. The specification teaches a variety of "stringent conditions" as "or those described in Nakayama et al" (see page 11). In absence of such guidance and/or working examples, one skilled in the art would reasonably conclude that a large number of DNA molecules would be able to hybridize, however, the specification has not taught how a representative number of the hybridizing molecules would encode the proteins.

Claims 12-13 are broadly drawn to a medicine comprising as an active ingredient the tumor antigen peptide. Enablement of a "medicine" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed medicine is for the treatment of autoimmune diseases and tumors.

Although the specification discloses the claimed medicine, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of autoimmune diseases and tumors.

At the time the invention was made, medicines comprising the claimed polypeptides were not routinely used for the treatment of autoimmune diseases and tumors. The specification lacks guidance by way of general methods or working examples which teach an amount of the polypeptide which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as treatment of autoimmune diseases and tumors. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed medicine effective for its intended use. Therefore, undue experimentation would be required to make and use the invention. Amending the claims to remove the term "medicine" and replace the term with "composition" would be sufficient to obviate this part of the rejection.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of variants encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 6-9 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakao et al (Cancer Res. 55:4248-4252, 10/1/95, IDS #2).

a. The claims recite a tumor antigen protein produced by expression of DNA of claims 1 or 2 or part of the protein which can bind to MHC class I antigen to be recognized by T cells which comprises all or part of amino acid sequence of positions 749-757, 736-744, 785-793, or 690-698, and compositions comprising such.

b. Nakao et al teach a peptide antigen expressed on SCC from KE-4 tumor cells (see page 4248 and Figure 3). Nakao et al teach KE-4 CTL, which is the same cells used by Applicants (see page 30 of specification) which lysed tumor cells when HLA A2601 cDNA was transfected (see page 4251). The method in which the peptides were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Thus, it is the Examiner's position that Nakao et al have produced an antigen that is expressed on SCC from HLA A2601 cDNA from KE-4 tumor cells and that this antigen has the same properties as that claimed in that it can bind to MHC class I antigen and which can be recognized by T cells. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antigen and the antigen of Nakao et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antigen and the antigen of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

11. Claims 7-8 and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsui et al (U.S. Patent 5,776,667, filed 6/6/95).

a. The claims have been described supra.

b. Tsui et al teach a polypeptide which comprises part of residues 785-793 of SEQ ID NO:2 and compositions comprising such (SEQ ID NO:41 of Tsui et al) (see attached sequence alignment on back of this Action Office. "Db" is sequence of Tsui et al and "Qy" is residues 785-793 of SEQ ID NO:2). Because the claims recite all or part of the amino acid sequence of 785-793, the art of Tsui et al reads on the claims. The method in which the peptides were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

12. Claims 6-9 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Boon et al (J. Exp. Med. 183:725-729, 3/1996, IDS #2).

a. The claims have been described supra.

b. Boon et al teach the MAGE protein which is recognized by T cells and can bind to MHC class I antigen. The protein of Boon et al is a variant of the claimed protein and peptides

and it would be inherent that the Boon et al protein would contain peptides that would also bind to HMC class I antigen and be recognized by T cells. The method in which the peptides were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Summary

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a

general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Application No.: 09/202,047

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [X] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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